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ATENT AND TRADEMARK OFFICE

F. FORNER et al.

October 15, 1996

On Application No. 08/437,682

Filing Date: May 9, 1995

For: INDOLE DERIVATIVES

Atty. Docket No. 31767-138142

CITATION OF

PRIOR ART

UNDER 35 U.S.C. § 301

October 21, 1999


Assistant Commissioner for Patents  
Washington, D.C. 20031

Sir:

Pursuant to 35 U.S.C. § 301 and 37 C.F.R. § 1.501(a), the patent owner submits the attached Citation of Prior Art and respectfully requests that it be entered in the official file of the patent. The Citation includes an explanation of pertinency and applicability and an explanation of how the claims differ from the prior art pursuant to 37 C.F.R. § 1.501(a).

It is not believed that any fees are required in conjunction with this submission. Should a fee be required, the Commissioner is hereby authorized to charge such fee to Deposit Account No. 22-0261

Respectfully submitted,

  
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IN THE UNITED STATES PATENT AND TRADE MARK OFFICE

In re PATENT NO. 5,565,447  
(Application Serial No. 08/437,682)

Issued to: Dolors Fernandez Forner *et al* )  
Filed: May 9th 1995 )  
Issued: October 15th 1996 )  
For: New Indole Derivatives )



CITATION OF PRIOR ART

Sir:

This Patent issued on 15th October 1996. Very recently, the Assignee of this Patent has become aware of a published German patent application DE-40 39 631 A1 published on 17th June 1992. The publication date of the German application is shortly before the 28th July 1992 priority date claimed in the application from which this Patent issued. A copy of this published German application is attached in accordance with 35 U.S.C. §301.

This published German application was not cited by the US Patent and Trademark Office Examiner during prosecution of the Patent application from which this Patent issued, nor was it cited by a Patent Office Examiner in the prosecution of any corresponding application in other countries.

For reasons that will be discussed in more detail below, the published German application is not regarded as pertinent prior art but, out of an abundance of caution, it is being drawn to the attention of the US Patent Office now with a request that this letter and the accompanying German Patent application be placed in the file wrapper of this Patent.

Patent No. 5,565,447 claims certain new indole derivatives of the general formula I (see claim 1). Insofar as it relates to the issue under discussion here, attention focuses upon the compounds of formula I of the issued US patent in which  $R^1$  and  $R^2$  are hydrogen or an alkyl group and Z represents a ring selected from II or IV. When Z is a ring of formula

II or IV (see claim 1), the sulfonamide substituent at position 5 of the indole ring is one in which the nitrogen of the sulfonamide group forms part of a piperidine ring or other 5, 6 or 7 membered rings.

DE-4 039 631A might be thought to disclose compounds of a similar structure to those of claim 1 mentioned above for this reason, and therefore might be thought to have a bearing on the patentability of claim 1. This German patent application is concerned with a composition of a 5-HT<sub>1A</sub> receptor agonist with a 5-HT<sub>2</sub> receptor antagonist. One of the components of this composition can be an indole of the formula given at the top of page 4 of the German text. In this page 4 formula, the aminoethyl substituent at position 3 on the indole ring is the same as the aminoethyl substituent at position 3 on the indole ring of formula I of US patent 5,565,447. In claim 1 of the US patent, the substituents on the amino group, R<sup>1</sup> and R<sup>2</sup>, can be hydrogen or an alkyl group. In the formula on page 4 of the German application, the substituents on the amino group, R<sup>6</sup> and R<sup>7</sup> are defined as:

"R<sup>6</sup> and R<sup>7</sup> are the same or different and are hydrogen or a lower alkyl (C<sub>1</sub> up to about C<sub>6</sub>) group,"

see the German text four lines below the formula at the top of page 4.

In this respect, the substituted indoles of the US patent and the German application are identical.

The substituent at position 5 of the indole ring in the formula at the top of page 4 of the German application is R<sup>8</sup>-(CH<sub>2</sub>)<sub>m</sub>- where m is defined as 1 (see definition two lines below the formula).

The group R<sup>8</sup> can be, for example, a group SO<sub>2</sub>NR<sup>2</sup>R<sup>3</sup> where R<sup>2</sup> and R<sup>3</sup> have the above given meaning, see the definition in line 3 after the formula at the top of page 4.

What we have so far is that the substituent at position 5 of the indole at the top of page 4 of the German application is a group -CH<sub>2</sub>-SO<sub>2</sub>NR<sup>2</sup>R<sup>3</sup>.

This needs to be compared with the substituent CH<sub>2</sub>SO<sub>2</sub>-Z in formula 1 of claim 1 of the issued US patent.

It is therefore necessary to determine how the German patent application defines the groups R<sup>2</sup> and R<sup>3</sup> in the section preceding the indole formula at the top of page 4 of the German application. This information is to be found in the German application on page 3 in lines 4 and 5 following the formulae at the top of page 3. This definition reads:

"R<sup>2</sup> and R<sup>3</sup> are the same or different and represent hydrogen or a C<sub>1-4</sub> alkyl group or

$R^2$  and  $R^3$  together with the carbon atom of the piperidine ring forms a cyclopentyl or cyclohexyl ring".

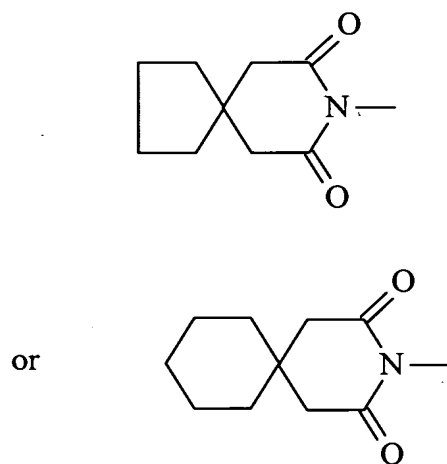
In the case where  $R^2$  and  $R^3$  in the German formula are hydrogen or an alkyl group, the  $CH_2SO_2R^2R^3$  substituent in the indole at the top of page 4 of the German application is an acyclic sulfonamide eg.  $CH_2SO_2NH_2$  or  $CH_2SO_2N(CH_3)_2$ .

Such acyclic sulfonamide residues are not and were never contemplated within the scope of the formula I of the issued US patent. The sulfonamide has always been defined with the formula  $SO_2Z$  where Z has always been a cyclic sulfonamide with the nitrogen atom forming the ring nitrogen of a piperidine, pyrrolidine, azepine, morpholine or piperazine ring system.

We must therefore look at the second definition of the  $R^2$  and  $R^3$  substituents of the German application. These are to be found in line 5 after the formulae at the top of page 3 of the German application which reads:

" $R^2$  and  $R^3$  together with the carbon atom of the piperidine ring forms a cyclopentyl or cyclohexyl ring".

Putting this definition into its correct context which is in the first formula at the top of page 3 of the German application, it will be seen that  $R^2$  and  $R^3$  together with the carbon atom of the piperidine ring would form a spiro ring system of the formula.



It is impossible to insert this definition into the formula of the indole substituent given at the top of page 4 of the German application. The substituent has to be -  $CH_2SO_2NR^2R^3$ . It is not possible, within the normal understanding of the theory of

chemical valency, to insert into this sulfonamide structure a definition of  $R^2$  and  $R^3$  which, together with the carbon atom of the piperidine ring would form a cyclopentyl or cyclohexyl ring. This definition is specifically focussed upon the spiro ring structure which arises from the first formula on the top of page 3 of the German application.

In other words, the most logical interpretation that one can give to the definition of the substituent  $-\text{CH}_2\text{SO}_2\text{NR}^2\text{R}^3$  where  $R^2$  and  $R^3$  are "as defined above" is that it is an acyclic sulfonamide which is not and never has been claimed in formula I of claim 1 of the US patent. More precisely, it is certainly not possible to identify in the German application any disclosure of compounds where the substituent at position 5 of the indole ring system is a cyclic sulfonamide of the type encompassed by formula I of claim 1 of the US patent where the nitrogen atom of the sulfonamide group forms part of a ring as defined in formula II, III, IV or V of the issued US patent.

Additional prior art mentioned in the DE 40 39 631 A1 does not support any other interpretations of the substituent  $-\text{CH}_2\text{SO}_2\text{NR}^2\text{R}^3$ . For example, EP-A 2 36 930, DE-A 31 31 728, DE-A 29 40 687 and DE-A 33 20 521 do not anticipate nor make obvious the cyclic sulfonamide containing structures of the US patent. In fact, the British equivalents of DE-A 31 31 728 and DE-A 33 20 521 (GB-A-208175 and GB-A-2124210, respectively) were cited in the International Search Report only as technological background to the invention (category "A"). Furthermore, the US patent was initially rejected as obvious over GB-A-208175 by the Examiner, but this rejection was overcome.

EP-A 2 36 930 and DE-A 29 40 687 relate to compounds which are structurally further removed from the compounds of the patent than the compounds in DE-A 31 31 728 (GB-A-208175) and DE-A 33 20 521 (GB-A-2124210) which have already been considered. EP-A 2 36 930 relates to aromatic 2-aminoalkyl-1,2-benzisothiazol-3(2H)-one-1,1-dioxide derivatives which may be substituted by a 3-(2-aminoethyl) indol radical via its aminoethyl group, the indol ring of the substituent may be further substituted by a hydroxy or methoxy group. DE-A 29 40 687 is equivalent to GB-A-2035310 and relates to indole-5-carboxamides and their thio analogues. These compounds are similar to the compounds disclosed in DE-A 31 31 728 (GB-A-208175) except that they necessarily have a carboxamide group  $(-\text{C}(\text{O})\text{N}=\text{})$  or a carbothioamide group  $(-\text{C}(\text{S})\text{N}=\text{})$  bound directly to the indol ring at the 5-position.

In order to ensure that all of the documentary requirements are fulfilled, a copy of

EP-A-0 236 930, DE-A 29 40 687 and GB-A-2035310 are attached.

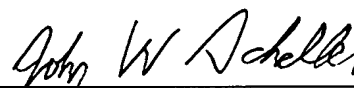
It should also be pointed out that neither DE-40 39 631 A1 nor patent documents DE-A 31 31 728, DE-A 33 20 521, EP-A-0 236 930 or DE-A 29 40 687 mentioned therein refer to any specific indoles that would fall within the indole definition at the top of page 4 and that would assist in interpreting the  $-\text{CH}_2\text{SO}_2\text{NR}^2\text{R}^3$  definition.

For these reasons, it will be recognised that, while the formula at the top of page 4 of the German application may initially have been thought to bear some structural resemblance to the indoles claimed in the US patent, a detailed analysis of the type given above clearly demonstrates that there is no disclosure of indoles having at position 5 a sulphonamidomethyl substituent where the nitrogen atom of the sulfonamide forms part of a ring system of the type shown in formula II, III, IV or V in claim 1 of the issued US patent.

For these reasons, it is believed that the German application should not be regarded as relevant prior art to this patent.

In accordance with 35 U.S.C. §301 the U.S. Patent and Trademark Office is respectively requested to place this paper together with the enclosed copy of DE 40 39 631 A1 in the public file of this issued patent so that it can be available to any member of the public who reviews the file wrapper.

Respectfully submitted,



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Date: